

## ORIGINAL ARTICLE

## Fatal asthma or anaphylaxis?

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The incidence of anaphylaxis is under-reported. Children with asthma are frequently atopic and prone to allergic reactions. Parents and clinicians may attribute wheeze of rapid onset to acute severe asthma, rather than recognising an anaphylactic event. Two cases of fatal anaphylaxis are reported who were initially diagnosed as acute severe asthma, and responded poorly to bronchodilator treatment. Survivors of "acute asphyxic asthma" should be screened for reactions to common allergens that provoke anaphylactic reactions. Even if no provoking factor is identified, the asthma management plan of children who survive an episode of acute asphyxic asthma should include intramuscular adrenaline (epinephrine) in addition to conventional bronchodilators.

Death from asthma in childhood is rare occurring in 1 in every 10 000 affected children.<sup>1</sup> While most deaths occur in children with severe asthma, it has been reported that sudden and unexpected death may occur in children with only mild disease.<sup>2</sup> In many cases of fatal asthma there is an identifiable trigger, delay in seeking medical attention is common, and a gradual decline over days culminates in a rapid deterioration in clinical status.<sup>2,3</sup> A predominance of respiratory symptoms in patients having an anaphylactic reaction may be misdiagnosed as acute asphyxic asthma.<sup>4–8</sup>

Two recent fatalities occurring at our hospital serve as a reminder that acute anaphylaxis in patients with asthma may go unrecognised.

**CASE 1**

A 4 year old boy was brought to hospital by ambulance, having suffered a cardiorespiratory arrest at home. He had asthma that was well controlled with occasional Salbutamol via inhaler and he had had no previous hospital admissions.

On the day of presentation, he appeared to choke after eating a meal of seafood and rapidly developed gasping respirations. He also had an episode of profuse diarrhoea. His parents gave Salbutamol via his inhaler and immediately summoned an ambulance, believing that their child was suffering an asthma attack.

The child became apnoeic and neighbours started CPR. On arrival of the paramedic crew, 30 minutes after the collapse, the child was asystolic and apnoeic. He was intubated in the field and managed according to standard ALS guidelines. Cardiac output was obtained within 45 minutes of the initial event. En route to hospital, the child required a further four doses of intravenous adrenaline (epinephrine) 0.1 ml/kg 1 in 1000 to alleviate bronchospasm.

He was apnoeic on arrival at the hospital. He was transferred to the paediatric intensive care unit (PICU) for mechanical ventilation and a dopamine infusion was added for further inotropic support.

Throughout the resuscitation, the child's pupils were fixed and dilated. In PICU, no spontaneous breaths were noted. Brain stem death was confirmed clinically and ventilation was ceased 16 hours after the respiratory arrest.

Significantly, his IgE concentration were increased (1271 kU/l) and mast cell tryptase level, taken over 12 hours after the anaphylactic event began, was 7.9 µg/l (range 0–15 µg/l). No definite trigger was found with RAST testing for crab, chicken, and peanut being negative. No necropsy was performed in accordance with the parents' wishes.

**CASE 2**

A 9 year old girl was diagnosed with asthma at 3 years of age and had required several hospital admissions when the family lived overseas. One admission necessitated intensive care, but the child had not been ventilated.

Five days before presentation, she developed coryzal symptoms and her general practitioner started cephalor suspension. Over the next two days, her cough and fever persisted and she became increasingly breathless, requiring admission to her local hospital on the third day of the illness. An urticarial rash was noted and was attributed to intravenous hydrocortisone, which had been administered for the wheeze. The urticaria abated after oral promethazine (Phenergan) and prednisone. The girl was discharged after 36 hours, with Salbutamol nebulisers every four to six hours, supplementing her inhaler. Her mother was also advised to stop the cephalor.

On the day of presentation to our hospital, her mother gave a dose of cephalor. Within 15 minutes of receiving the antibiotic, the child complained of abdominal pain and then vomited, accompanied by diarrhoea. She became increasingly short of breath and collapsed. Her mother initiated CPR and the child was unconscious for 20 minutes until the paramedic crew arrived.

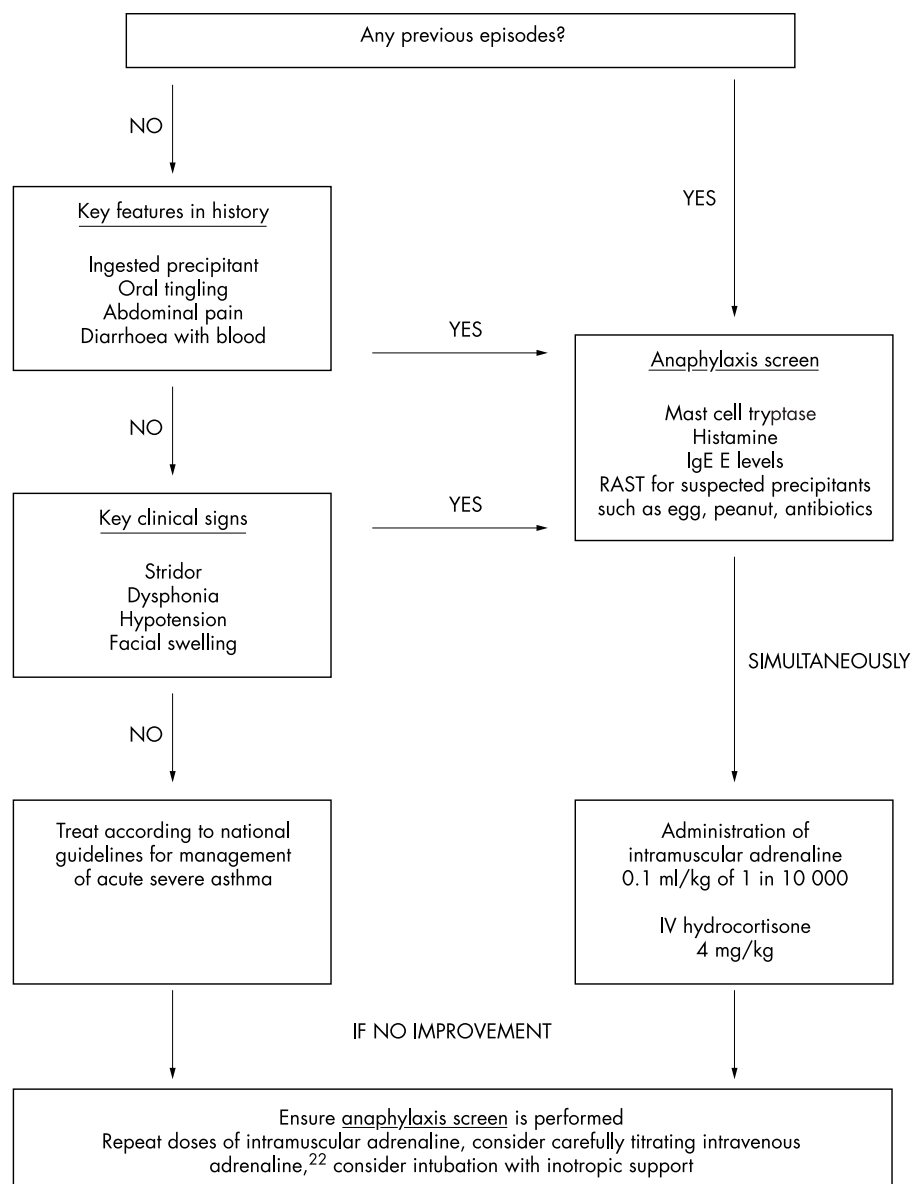
She was intubated and was asystolic, being managed according to standard ALS guidelines. Nine minutes into the resuscitation, she developed ventricular fibrillation and received 100 J DC shock. She then went from electromechanical dissociation to sinus bradycardia and received three doses of intravenous adrenaline 0.1 ml/kg of 1 in 1000 and one of intravenous atropine 20 µg/kg. On arrival at hospital, she was breathing spontaneously but her chest was noted to be hyper-expanded with bilateral reduction of air entry. No urticaria was noted before or after the administration of intravenous hydrocortisone. A Salbutamol infusion was started before transfer to PICU. Her pupils were fixed and dilated from the time of arrival in the emergency department and her gag reflex was also noted to be absent.

There was no improvement in clinical status despite ventilation and intravenous bronchodilators with corticosteroids. The clinical finding of brain stem death was confirmed by a cerebral perfusion scan. Care was withdrawn in accordance with the parents' wishes.

Her IgE was increased (765 kU/l) and RAST for amoxycillin, cephalothin and cephalor were weakly positive. RAST for cephalixin was equivocal. A necropsy was not performed in respect of the parents' cultural beliefs.

**DISCUSSION**

The cases presented in this report highlight that the diagnosis of anaphylaxis is often overlooked in children with asthma.



**Figure 1** Model for distinguishing acute severe asthma and anaphylaxis.

The classic clinical picture of anaphylaxis has an acute precipitous onset, such as in case 1 but a multiphasic reaction such as in case 2, is not unusual.<sup>9-10</sup> Only the diverse associated symptoms, such as gastrointestinal disturbance, can alert the clinician to distinguish anaphylaxis from asthma. The reported incidence of anaphylaxis in populations ranges from 3 to 30 per 100 000, which suggests that many cases are not identified.<sup>11-12</sup> Rapid recognition of symptoms of anaphylaxis could prevent such cases becoming fatalities.

There are four lessons to be drawn from these cases.

Firstly, when dealing with a child with rapid onset of wheeze or one who is slow to respond to bronchodilators, clinicians should enquire about the subtle features of anaphylaxis.

Secondly, the usual triggers for anaphylaxis are medications and foodstuffs. Clinical suspicion may be confirmed by specific radioimmunoassay (RAST) and mast cell tryptase levels.

Thirdly, where anaphylaxis is suspected, the early use of adrenaline, whether intramuscular or intravenous in extremis, is mandatory.

Finally, children with features of acute asphyxial asthma should be screened for allergens and should have intramuscular adrenaline as an element in their asthma management plans.

### Distinguishing anaphylaxis from acute severe asthma

When faced with a child with features of acute asphyxial asthma, anaphylaxis should be suspected when urticaria develops along with wheeze and hypotension.

Confirmatory investigations exist such as immunoglobulin E concentrations, RAST for possible triggers, histamine, and mast cell tryptase. Although mast cell tryptase is not widely available, and its role as a routine diagnostic test is still under investigation, as shown in this paper, it may be useful in diagnosis in selected cases. If mast cell tryptase is available, it must be taken within six hours of the first signs of allergic reaction, otherwise the levels return to normal.<sup>9</sup> However, in anaphylactoid reactions mast cell tryptase levels may not be increased.<sup>13</sup> Moreover, ingested allergens tend not to provoke such a marked rise in mast cell tryptase.<sup>8</sup> However, a protracted increase in histamine levels may further distinguish food induced anaphylaxis from acute asphyxial asthma.<sup>14</sup> Ideally, these tests should be performed on all who suffer acute asphyxial asthma and those who suffer from acute severe asthma, which is slow to respond to maximal bronchodilator therapy (fig 1). Further distinction of anaphylactic reactions from asthma can be made from postmortem histological examination<sup>6-7</sup> thereby improving the reporting of the disorder.

### Identifying precipitants of an anaphylactic reaction

Mild anaphylactic reactions in children are difficult to recognise as symptoms such as runny nose, cough, or vomiting is often attributed to a viral illness, which in turn causes wheeze. Moreover, children often get urticarial reactions with illness, for example, herpes simplex virus, *Mycoplasma pneumoniae*. With widespread antibiotic use for upper respiratory tract infections, an urticarial rash may be attributed either to the illness or to the gradual evolution of sensitisation to the antibiotic. Thus the presence of antibiotic allergy may not be clearly recognised, such as in case 2.

Antibiotics are one of the major contributors to drug hypersensitivity. It is estimated that 6%–15% of hospitalised patients experience some sort of adverse drug reaction,<sup>15</sup> ranging from rash; a serum sickness-like reaction; drug fever; to pulmonary, hepatic, and renal involvement; as well as systemic anaphylaxis.

The prevalence of peanut allergy is concerning as peanut oil is frequently used in cooking and food preparation. Clinicians dealing with possible anaphylactic reactions should inquire not only about the food contents, but also how the food has been prepared.

### Adrenaline for acute asphyxial asthma

The importance of adrenaline in the treatment of anaphylaxis is undisputed.<sup>16–17</sup> The role of adrenaline in acute asthma was debated throughout the 1980s and subcutaneous adrenaline was gradually supplanted by nebulised  $\beta_2$  agonists such as Salbutamol. Yet adrenaline remains in the management plan of adult sufferers of acute asphyxial asthma.<sup>4–5, 18</sup> A provoking allergen may not always be identified but their rapid and catastrophic deteriorations are so similar to anaphylaxis. Moreover, without knowing the trigger of the deterioration, the episodes frequently recur. Significantly, the British guidelines for the management of asthma in children do not have a role for intramuscular adrenaline.<sup>19</sup> The Australian guidelines include adrenaline only if the contribution of anaphylaxis to the episode of acute severe asthma is recognised.<sup>20</sup>

Survivors of acute asphyxial asthma should be prescribed self administering adrenaline devices, along with Medic alert bracelets. Before issuing pre-loaded syringes, the clinician must demonstrate their use. In our series of 61 children presenting with urticaria, two children had their own pre-loaded adrenaline delivery devices, because of previous anaphylactic reactions. However, one child had not received a dose before presenting at hospital because the parents were unfamiliar with its use. This is a recurring theme.<sup>21</sup>

### Summary

Patients who have symptom of acute severe asthma may in fact be suffering from anaphylaxis. We propose the scheme in figure 1 to improve detection of children suffering from anaphylaxis. Specific questioning may elicit subtle symptoms of anaphylaxis and exposure to common allergens. The diagnosis may be confirmed by mast cell tryptase levels, but only when taken proximate to the onset of the reaction. Allergens can be identified by RAST or skin prick testing. Finally, survivors of an episode of acute asphyxial asthma should be

considered for the issue of self administering adrenaline devices, as the episodes are likely to recur. Use of the devices must be demonstrated so that the patient or their carers can use them competently. The patient should also be advised to wear a Medic Alert bracelet. Such measures are likely to ensure that fatalities such as those presented here are less likely to occur.

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